THE EFFECT OF GLYCEROL ON THE REDUCTION OF OXIDATIVE DEGRADATION IN SHAPE MEMORY POLYMER FOAMS

An Undergraduate Research Scholars Thesis

by

GARRETT HARMON

Submitted to the Undergraduate Research Scholars program
Texas A&M University
in partial fulfillment of the requirements for the designation as an

UNDERGRADUATE RESEARCH SCHOLAR

Approved by
Research Advisor: Dr. Duncan Maitland

May 2016

Major: Biomedical Engineering

TABLE OF CONTENTS

ABSTRACT

The Effect of Glycerol on the Reduction of Oxidative Degradation in Shape Memory Polymer Foams

Garrett Harmon
Department of Biomedical Engineering
Texas A&M University

Research Advisor: Dr. Duncan Maitland
Department of Biomedical Engineering

A biocompatible shape memory polyurethane foam device has been developed as a treatment for neurovascular aneurysm occlusion. Polyurethanes are extensively utilized in biomaterials due to their biocompatibility and easily customizable traits. The synthesis of the proposed polyurethane-based SMP device includes triethanolamine (TEA), which incorporates a nitrogen into the polymer backbone. The nitrogen promotes oxidative degradation initiation in the presence of reactive oxygen species (ROS). Oxidative degradation could result in the chemical breakdown of the polymer chain and the potential production of harmful by-products from the material. In the present research, foams were synthesized using glycerol in place of TEA to evaluate a means to reduce oxidative degradation. After addition of glycerol, foam characterization showed that physical traits and thermal responses were retained and mechanical properties were improved relative to foams synthesized with TEA. Accelerated degradation studies demonstrated a decreased rate of oxidative degradation with increasing glycerol concentration. Overall, replacement of TEA with glycerol provides a polyurethane foam with reduced oxidative degradation while retaining the desired physical and thermal characteristics.

ACKNOWLEDGMENTS

I would like to thank Dr. Duncan Maitland for his tremendous support and this wonderful opportunity. I would also like to thank Dr. Mary Beth Browning Monroe, Dr. Brandis Keller, Grace Fletcher, Sayyeda M. Hasan, and Andrew Weems for providing input and guiding my thought process to help me become a better researcher and student. Finally, I would like to thank all members of the biomedical device laboratory for further information that shaped this project.

NOMENCLATURE

FDA	Food and Drug Administration
SMP	Shape memory polymer
T_g	Glass transition temperature
TEA	Triethanolamine
ROS	Reactive oxygen species
HPED	N, N, N', N'-tetrakis(2-hydroxypropyl)ethylenediamine
TMHDI	trimethyl-1,6-hexamethylene diisocyanate
DI	Deionized
NCO	Isocyanate group
OH	Hydroxyl group
IPA	Isopropyl alcohol
SEM	Scanning electron microscopy
ATR-FTIR	Attenuated total reflectance Fourier transform infrared
DSC	Differential scanning calorimetry
ASTM	American Society for Testing and Materials
MTS	Mechanical testing system

CHAPTER I

INTRODUCTION

A cerebral aneurysm is the local ballooning of an arterial wall in the brain. These dilations can be the result of a number of arterial conditions, including intravascular plaque build up, a weakened arterial wall, or severe vessel injury following trauma to the head[1]. Once the vasculature expands, it becomes weak and thin, making it susceptible to rupture and hemorrhage inside the subarachnoid space. Subarachnoid hemorrhage occurs in approximately 1 in 10,000 people annually in the United States[2]. Due to the large affected population and high morbidity and mortality of brain hemorrhage, there is an urgent clinical need for a safe and effective a treatment to prevent subarachnoid aneurysm rupture.

Currently, only a few FDA approved treatments are available for cerebral aneurysms. One method is surgical clipping of the aneurysm, which requires a craniotomy, a highly invasive surgery where the skull is opened to allow access to the brain. The aneurysm is isolated from blood flow using a clip that is placed around its neck[3]. This procedure is highly successful but has limitations based on aneurysm location and size. These factors can make this method of treating cranial aneurysms difficult and highly risky[4]. Another approved method of endovascular treatment involves inserting thin bare platinum coils into the aneurysm via a micro catheter[3]. The dense network of coils promotes clotting through electrolysis to encourage blood aggregation. This process occludes the aneurysm and allows for laminar blood flow to resume after a new layer of endothelial cells grows over the aneurysm opening. While endovascular coils encourage blood clotting within the aneurysm, there are drawbacks to this

approach; because electrolysis is weak and the coils are bare, blood does not readily clot, and complete occlusion often takes a long time. Likewise, small protrusions of the coils into the arterial lumen can damage the vasculature and cause incomplete occlusion through a disruption of endothelial cell recovery[5]. These issues result in a longer healing time and ineffective treatment for the patient.

Recently, a biocompatible shape memory polyurethane foam device has been developed to use in conjunction with platinum coils to enhance aneurysm occlusion and restore laminar flow[6]. Shape memory polymer (SMP) foams are a class of smart material that can be designed in a primary orientation and subsequently deformed and stored in a secondary orientation. With the application of an external stimulus, they return to the primary orientation. In this system, the shape memory effect is achieved by heating the material above its glass transition temperature (T_g) and applying a deforming stress. When the material is above its T_g, the polymer chains can move freely into a secondary shape that is maintained once the material cools until it is re-heated above its T_g. Then the material will return to its primary low energy orientation[7]. For this specific application, polyurethanes were selected for use in SMP foams due to their biocompatibility and desirable mechanical and thermal properties[8]. Foams are heated and crimped in order to be implanted into an aneurysm via micro catheter. Once implanted, the foam begins to expand to its original diameter when heated to above its T_g at body temperature[6]. When expansion is complete, the foam fills the aneurysm to promote blood clotting and complete occlusion[6].

While the current SMP foams show promise as a viable alternative in the treatment of intracranial aneurysms, some limitations are present that could reduce the device's effectiveness. One limitation is the foam's susceptibility to oxidative degradation. Oxidative degradation occurs due to a reaction between oxygen in physiological environments and the polyurethane backbone[10]. The oxygen reacts with branch points on the polymer chain, which break down to weaken the stable polymer structure. This chemical reaction is initiated through interactions between oxygen and hydrogens on side and end groups on the polymer branches[10, 11]. Once initiated, these interactions continue to propagate and degrade the device further, which could potentially result in harmful by-products, ineffective blood clotting, or early device failure.

In industry, oxidative degradation is prevented through the integration of antioxidants in the polymer. Antioxidants trap free radicals to prevent oxidative degradation initiation and propagation[11]. As degradation occurs, there is an aggregation of free radicals from the physiological environment. These free radicals attack the weakest bonds in the polymer chain and encourage further degradation[11]. While the addition of antioxidants can offer a solution to oxidative degradation, their use increases device costs and is dependent upon uniform dispersion of the antioxidant within the polymer prior to curing, which would require significant design changes and could delay commercialization.

The objective of this project is to design a SMP device for intracranial aneurysm treatment that is chemically resistant to oxidative degradation. The monomers that make up the polymer chain can be adjusted to decrease susceptibility to oxidative degradation. Here, the chain structure will be altered to decrease interactions with oxygen. Currently, triethanolamine (TEA) is the triol used in

the polyurethane foam device synthesis. Preliminary research indicates that the nitrogen in TEA is the source of oxygen interaction, resulting in oxidative degradation. We hypothesize that glycerol can be used in place of TEA to synthesize SMP foams that are resistant to oxidative degradation while maintaining other desirable foam properties. Reducing oxidative degradation should decrease the amount of potentially harmful by-products and increase device lifespan, thereby enhancing the safety and efficacy of the aneurysm filling device.

CHAPTER II

METHODS

SMP Foam Synthesis

The chemicals used in foam synthesis are: N, N, N', N'-tetrakis(2-hydroxypropyl)ethylenediamine (HPED, 99%; Sigma-Aldrich Inc., St. Louis, MO), glycerol (99%, Sigma-Aldrich Inc., St. Louis, MO), trimethyl-1,6-hexamethylene diisocyanate (TMHDI, TCI America Inc., Portland, OR), Enovate 245fa blowing agent (Honeywell Innternational, Inc., Houston, TX), deionized (DI) water, T-131 (Air Products and Chemicals, Inc., Allentown, PA), BL-22 (Air Products and Chemicals, Inc., Allentown, PA), DC 198 (Air Products and Chemicals, Inc., Allentown, PA), and DC 5943 (Air Products and Chemicals, Inc., Allentown, PA).

To synthesize the SMP foam, an isocyanate (NCO) premix was made by mixing HPED, glycerol, and THMDI with excess NCO. This mixture was allowed to react for 36 hours. During the first 12 hours the mixture was heated to 50°C in an oil bath while mixing at 400 rpm to prevent glycerol from settling out of the solution. After 12 hours, the mixing was stopped, and the solution was removed from the oil bath and reacted for an additional 24 hours at room temperature. Then, a hydroxyl (OH) mixture was made using the remaining stoichiometric amounts of HPED and glycerol along with DI water and catalysts. The NCO premix, surfactants, and OH mixture were mixed together in a FlackTek speedmixer (FlackTek, Inc., Landrum, SC) at 3540 rpm for 20 seconds. One milliliter of Enovate was added, and the mixture was mixed at 3540 rpm at 5 seconds intervals until desired consistency was achieved. The mixture was then

poured onto a clean plastic sheet and placed into an oven at 90°C for 20 minutes to cure. After curing, the foam was cooled for 20 minutes before cleaning and further processing.
For this study, SMP foams were synthesized with glycerol:TEA mole ratios of 0:100, 20:80, 40:60, and 60:40 (0%, 20%, 40%, and 60%, respectively).

Foam Cleaning

Once the foams cooled, uniform foam blocks were cut and compressed at 90°C using a carver press (Carver, Inc., Wabash, IN). The foams were sonicated for one 15 minute cycle in DI water and then in isopropyl alcohol (IPA) for two consecutive 15 minute cycles, replacing IPA between cycles. After the two cycles of IPA, foams were sonicated in reverse osmosis (RO) water for approximately six 15 minute cycles, or until IPA was fully removed. After sonication, the foams were freeze dried and then placed in a vacuum oven at 50°C for 24 hours.

Foam Density

Three foam cubes were cut using a foam cutter from a uniform portion of the cleaned bulk foam. Using calipers, three measurements each for length, width, and height were taken, and the mass of the foam block was measured using a gravimetric scale. Using measurements from all three samples, an average density was calculated in g cm^{-3}.

Pore Morphology

Pore size and cell structure were determined by cutting thin foam slices in the axial and transverse directions. Using carbon tape, the cross sections were placed onto scanning electron microscopy (SEM) stubs and dried under vacuum overnight. The samples were sputter-coated

with gold for 60 seconds at 20 mA with a Cressington sputter coater (Ted Pella, Inc., Redding, CA). Using a Joel Neoscope JCM-5000 SEM (Nikon Instruments, Inc., Melville, NY) at 10 kV, images were taken at 20X magnification.

SEM images were analyzed using ImageJ software (NIH, Bethesda, MD). Ten pore diameter measurements were taken in both the axial and transverse directions and compared to determine average pore size (microns) and pore isotropicity between the axial and transverse directions.

Chemical Characterization

A small sample of clean and dried foam was cut from each glycerol foam composition, and the attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra was collected using a Bruker ALPHA Infrared Spectrometer (Bruker, Billerica, MA). Sixty-four background scans were run with no sample present followed by 32 scans of foam samples. Three absorbance spectra were collected for each composition at a resolution of 4 cm^{-1}. OPUS software (Bruker, Billercia, MA) was used to normalize spectra and correct baselines to enable comparison between foam compositions with different amounts of glycerol.

Thermal Transitions

Dry Differential Scanning Calorimetry (DSC)

Three foam samples per composition (2-5 mg) were dried under vacuum at 55°C overnight. After the samples were dried, they were weighed and placed in an aluminum pan and sealed with an aluminum lid. A Q-200 DSC (TA Instruments, Inc., New Castle, DE) was used to obtain thermograms for each foam sample through a series of two cycles. In the first cycle, temperature

was decreased to -40°C at a rate of 10°C per minute and maintained at -40°C for 2 minutes. Then, temperature was increased to 120°C at a rate of 10°C per minute and maintained for 2 minutes. The second cycle was a repeat of the initial cycle without the final hold at 120°C. Using TA instruments software, the T_g was found by analyzing the inflection point on the thermogram from the second cycle.

Wet DSC

Five samples (2-5 mg) were weighed and placed in a 50°C water bath for five minutes to fully plasticize. Excess water was removed by placing the samples in a Kimwipe (Kimberly-Clark Professionals, Roswell, GA) and applying pressure. The samples were re-weighed, placed in an aluminum pan, and sealed with a vented aluminum lid. Thermograms were obtained for each sample using the Q-200 DSC to cool the sample to -40°C at a rate of -10°C per minute, maintaining -40°C for 2 minutes, then heating the samples to 80°C at a rate of 10°C per minute. Using TA instruments software, the wet T_g after plasticization was found by analyzing the inflection point on the thermogram.

Volume Expansion and Recovery

Three foam cylinders (3 mm diameter, 1 cm length) were cut and placed on a 203.20 µm diameter nickel-titanium (nitinol) wire (NDC, Fremont, CA). The samples were radially crimped to the smallest possible diameter using a ST 150-42 stent crimper (Machine Solutions, Flagstaff, AZ) by equilibrating them in the uncompressed crimper at 100°C for 15 minutes, applying the crimper, and turning off the heater to allow the foam to cool to room temperature in the crimped state. Once crimped, an initial picture was taken using a digital Canon PowerShot SX230HS

camera (Canon, Melville, NY), and the samples were placed in a water bath at 40°C for 15 minutes and then at 50°C for 15 minutes. Pictures were taken every minute for 30 minutes. Foam diameters throughout the experiment were calculated using ImageJ software. Volume expansion and volume recovery were calculated from diameter measurements.

Mechanical Properties

Ten thin foam slices (3 mm) were made, and dog bone-shaped samples were cut according to ASTM 638 standards (Pioneer-Dietecs, Weymouth, MA). Wooden end pieces were attached to the samples using a quick set epoxy and left overnight to dry in a vacuum chamber. Sample widths were measured, and uniaxial tensile tests were run using an Insight 30 Material Tester (MTS) (MTS System Corporation, Eden Prairie, MN). The samples were held in the machine by the wooden end pieces. A constant strain rate of 5 mm/minute was applied at room temperature until sample fracture as a stress-strain curve was obtained. Using MatLab software (Mathworks, Natick, MA), the stress-strain data was analyzed to determine tensile strength (kPa), Young's modulus (kPa), strain at break (%), fracture point (mm), and toughness ($J\ m^{-3}$).

Accelerated Degradation

Twenty one foam cubes per glycerol composition (1 cm length, 1 cm width, 1 cm height) were weighed and placed in vials. An accelerated oxidative degradation solution was prepared (0.2 M $CoCl_2$ in 20% H_2O_2) and added to the foam vials, which were placed in an environmental chamber at 37°C. Every 2 days, three samples per composition were removed and sonicated in ethanol for 10 minutes. Then, the foams were sonicated in water for 10 minutes and dried under

vacuum at 55°C overnight. Dried samples were weighed to determine mass loss to assess the degradation progress.

CHAPTER III

RESULTS AND DISSCUSSION

Foam Density

Figure 1 shows the densities of the foam compositions analyzed. Average densities for 0%, 20%, 40%, and 60% glycerol were found to be 0.045 ± 0.002, 0.032 ± 0.002, 0.034 ± 0.001, and 0.038 ± 0.002 $g*cm^{-3}$ respectively (n = 3). Overall, the average density decreased with the incorporation of glycerol (Figure 1). Overall, these results demonstrate that the foam ultra-low density is maintained with the addition of glycerol.

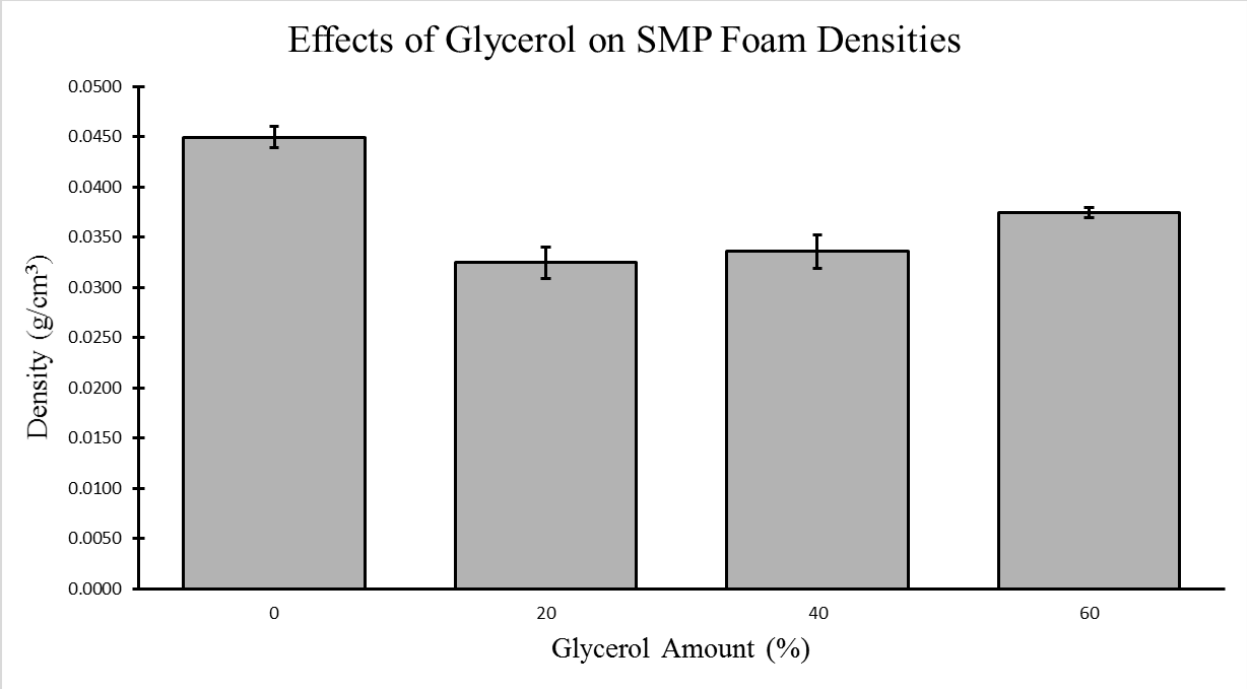

Figure 1. Average densities of 0%, 20%, 40%, and 60% glycerol foams. Mean ± standard deviation displayed; n = 3.

Pore Size and SEM

SEM imaging revealed that the average pore size for all compositions remained relatively constant (Table 1). As glycerol concentration increases, pore size decreases slightly. This decrease in pore size corresponds to small density increases with increasing glycerol concentration (Figure 1). These results demonstrate that the addition of glycerol does not require an adjustment in foaming factors to maintain consistent pore sizes. Additionally, Table 1 shows that pore diameter measurements are very similar in the axial and transverse directions, indicating that glycerol incorporation does not adversely affect foam isotropicity. This trend can be quantitatively seen in the SEM images of 0%, 20%, 40%, and 60% glycerol foams in the axial and transverse directions (Figure 2). As concentration of glycerol increases (left to right) pore size and isotropicity remain consistent.

Table 1. Pore sizes of SMP foams with increasing glycerol concentration.

Foam Composition (% Glycerol)	Imaging Direction	Pore Diameter (μm)	Isotropicity (Axial/Transverse)
0%	Axial	420 ± 100	1.11
	Transverse	380 ± 60	
20%	Axial	360 ± 40	0.87
	Transverse	410 ± 40	
40%	Axial	380 ± 20	0.93
	Transverse	410 ± 60	
60%	Axial	360 ± 30	0.94
	Transverse	390 ± 40	

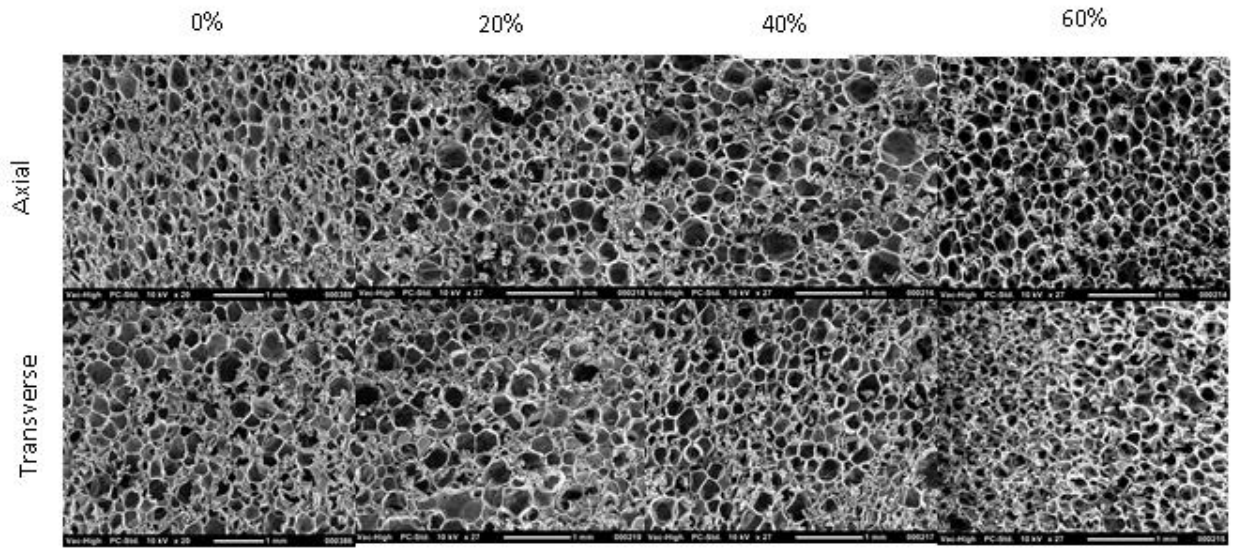

Figure 2. SEM images of 0%, 20%, 40%, and 60% glycerol foams in the axial and transverse directions.

Chemical Characterization

Analysis of the FTIR spectra (Figure 3) shows various peaks associated with polyurethane. The urethane C=O stretch (1698 cm^{-1}) confirms the presence of urethane. A small urea C=O (1647 cm^{-1}) shoulder is present due to the reaction of isocyanates with water during the foam synthesis. A decrease was observed in the amine peak (3330 cm^{-1}) due to a replacement in secondary amines as TEA concentrations decrease. These secondary amines are replaced with carbon in glycerol, which is shown in an increased carbon stretch peak (1252 cm^{-1}). Decreases in C-N bonds and increases in C-C bonds indicate successful glycerol incorporation into the SMP foam.

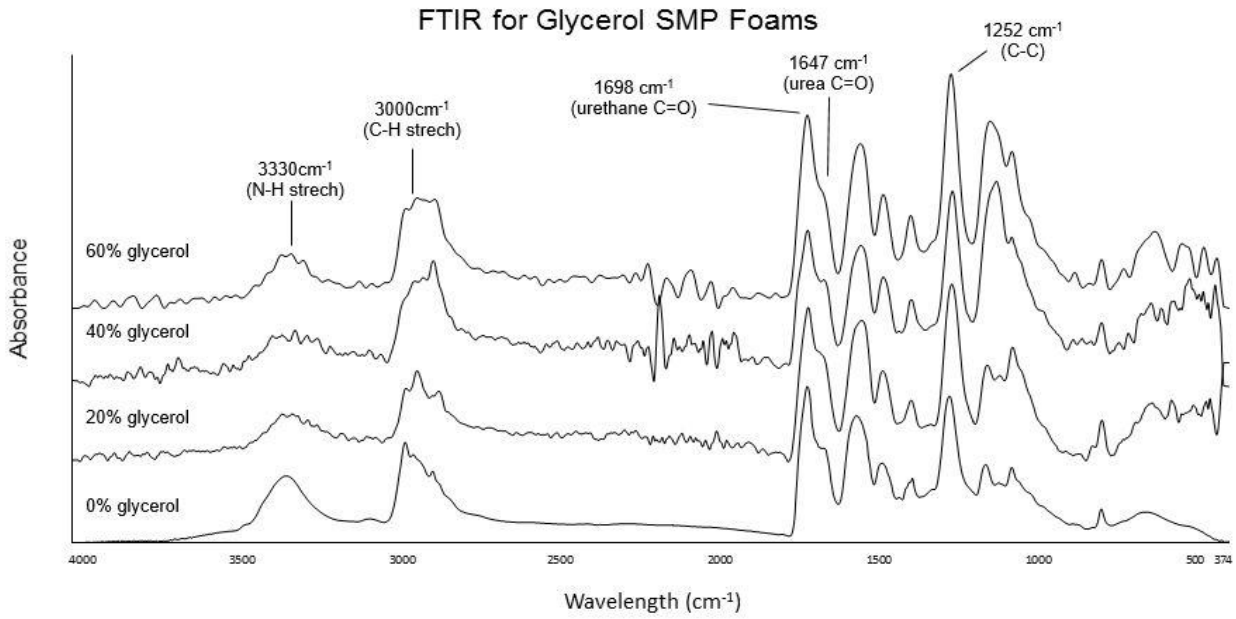

Figure 3. FTIR spectra of SMP foams with 0%, 20%, 40%, and 60% glycerol.

Thermal Transitions

Thermal analysis of the foams indicated that thermal transition temperatures were maintained with the addition of glycerol. Both dry and wet T_g averaged 67ºC and 44ºC, respectively (Figure 4). Incorporation of glycerol results in a polymer structure that is similar to that of TEA-based foams in terms of crosslink density, branching, and side groups. Structural similarity between compositions leads to similar heat input needed to transition from the glassy to rubbery state, resulting in similar T_g between TEA and glycerol foams.

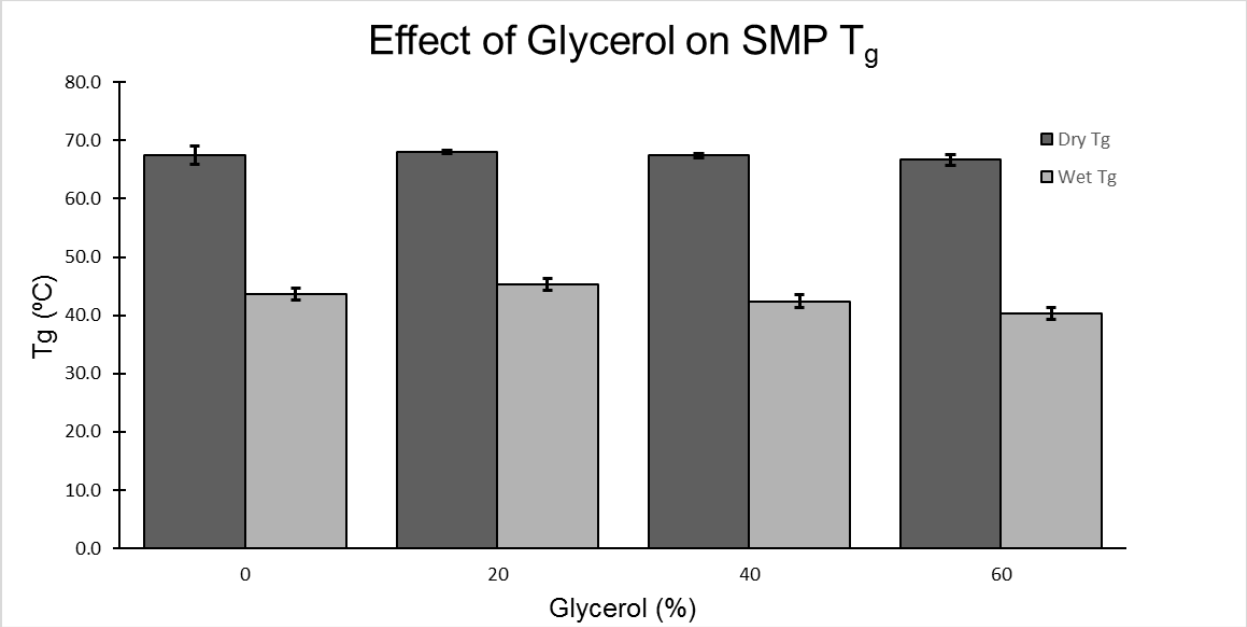

Figure 4. Dry and wet T_g of glycerol foams at 0%, 20%, 40%, and 60% glycerol. Mean ± standard deviation displayed; n = 3.

Volume Expansion and Recovery

Average volume recoveries of the 0% (control), 20%, 40%, and 60% glycerol foams were 62%, 133%, 142%, and 102%, respectively. The foams did not expand over 15 minutes at 40ºC; however, they expanded readily at 50ºC (Figure 5). Overall, glycerol foams showed faster expansion rates and larger volume recoveries compared to TEA foams.

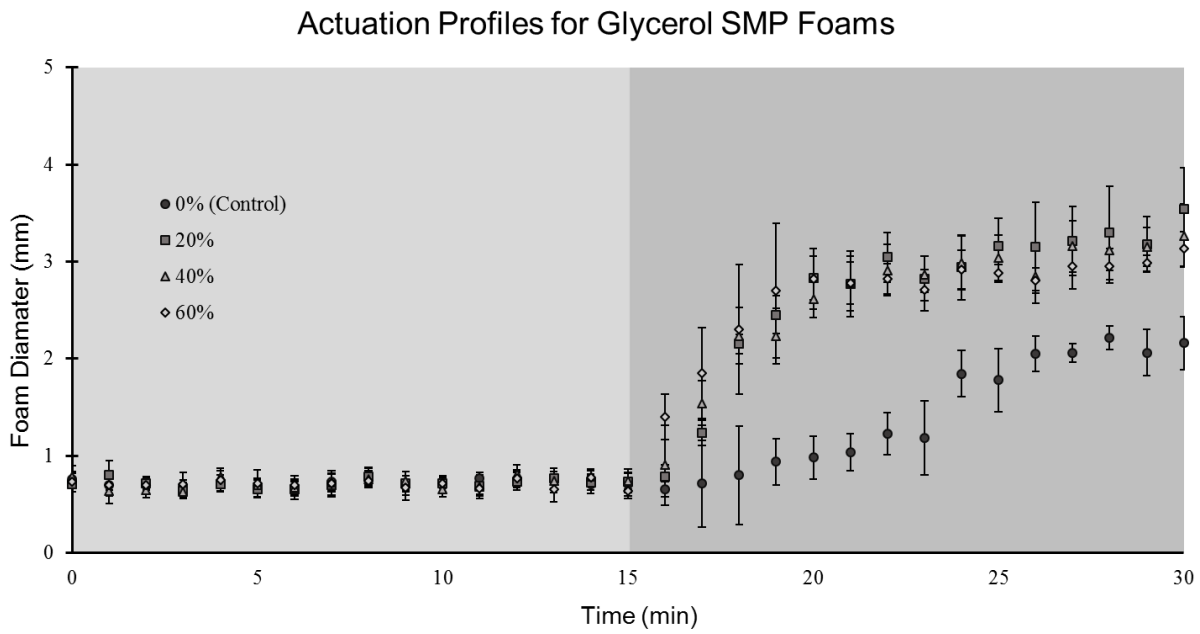

Figure 5. Volume expansion of 0%, 20%, 40% and 60% glycerol foams. Mean ± standard deviation displayed; n = 3.

Mechanical Properties

Glycerol incorporation into SMP foams had an effect on the mechanical properties. An observed increase in both toughness and ultimate tensile strain was observed (Table 2). Increases in strength and toughness indicate a decrease in polymer chain flexibility due to greater steric hindrance of closely packed hydrogen atoms and urethane groups and/or increased crosslink density with the incorporation of a smaller triol crosslinker. The smaller glycerol molecule results in closer proximity of hydrogen atoms and urethane groups which, as the chain is deformed, resist each other and try to maintain orientation. This restriction of movement results in a less ductile but tougher material with higher ultimate tensile strength.

Table 2. Young's Modulus, ultimate tensile strength, toughness, and strain at break in 0%, 20%, 40%, and 60% glycerol foams. Mean ± standard deviation displayed; n = 10.

Glycerol (%)	Modulus (kPa)	Ultimate tensile strength (kPa)	Toughness ($J*m^{-3}$)	Strain at break (%)
0 (control)	1250 ± 40	76 ± 10	18 ± 3	32 ± 4
20	2920 ± 220	160 ± 54	44 ± 18	33 ± 4
40	2100 ± 190	187 ± 41	51 ± 10	31 ± 7
60	2420 ± 90	188 ± 20	51 ± 5	34 ± 3

Accelerated Degradation

The reactive oxygen species (ROS) in the 0.2 M $CoCl_2$ in 20% H_2O_2 accelerate degradation processes *in vitro* to provide an indication of the long-term degradation profile of biomaterials. Overall, oxidative degradation decreased with increasing glycerol concentrations (Figure 6). Mass loss over time is reduced as glycerol concentrations increase from 0% (control) to 60%. Foams synthesized using TEA contain nitrogen linkages in the branch points, while glycerol provides carbon branch points. Nitrogen is more electronegative than carbon, and is therefore more susceptible to ROS-initiated oxidative degradation. The lower electronegativity of carbon provides oxidative degradation resistance, indicating that glycerol can be utilized to provide SMP foams with improved biostability.

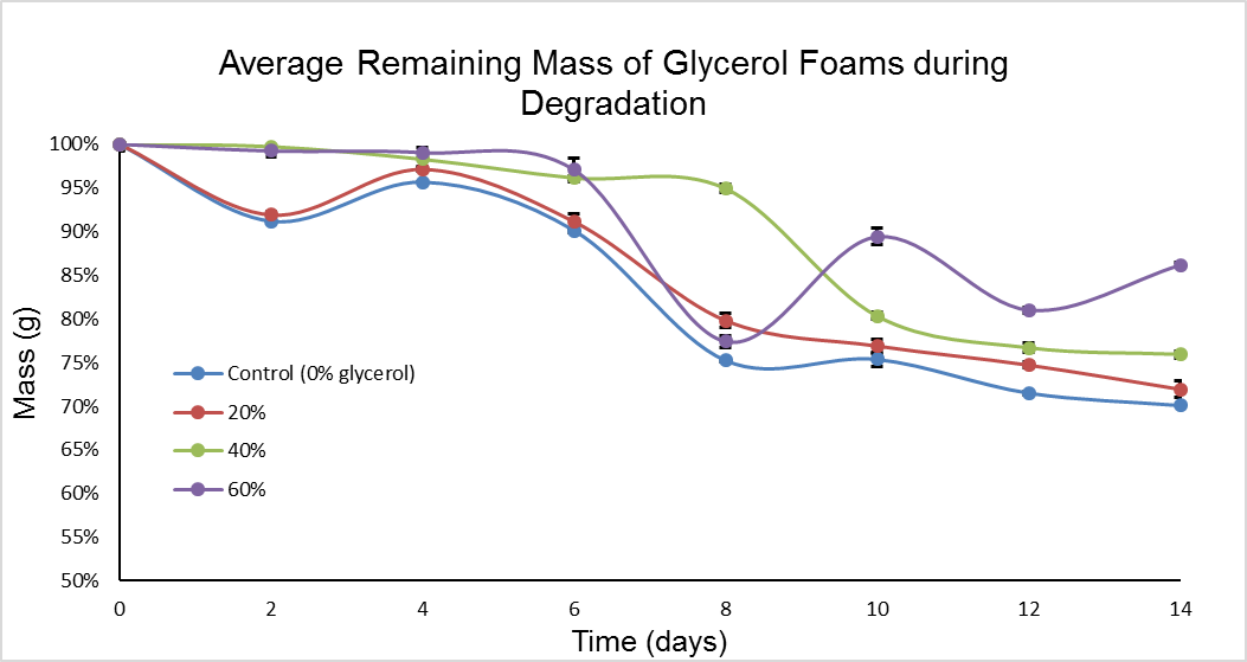

Figure 6. Mass remaining of 0%, 20%, 40%, and 60% during accelerated degradation in 0.2M $CoCl_2$ in 40:60 H_2O_2:H_2O solution. Mean ± standard deviation displayed; n = 3.

CHAPTER IV

CONCLUSION

Overall, the physical characteristics of foams synthesized with glycerol in place of TEA, such as density and pore size, remained consistent, while mechanical properties, including ultimate tensile strength and toughness, were improved. These results indicate that glycerol-based foams can be utilized in place of TEA-based foams with minimal design changes to provide similar device size and function.

Similarly, thermal characteristics of foams synthesized with glycerol remained consistent with those of TEA. This outcome provides predictable volume expansion and recovery times that are comparable to current TEA foams which have been previously optimized for use in delivery in cerebral aneurysms.

Finally, glycerol foams decreased oxidative degradation rates compared to TEA foams, potentially providing a safer, more effective device with an extended lifetime.
Future studies will include a real-time oxidative degradation study in 3% H_2O_2 and a hydrolytic degradation study in PBS (real-time) and 0.1M NaOH (accelerated). Other monomers with fewer electronegative atoms and/or antioxidants could be used to further reduce SMP foam oxidative degradation.

In conclusion, the hypothesis stating that glycerol could be utilized to reduce SMP foam oxidative degradation was tested and confirmed while the foam physical, mechanical, and

thermal properties were maintained or improved. These findings indicated that a safer, biostable cerebral aneurysm occlusion device may be achieved through incorporation of glycerol in place of TEA.

REFERENCES

[1] Etminan, Nima et al. “Cerebral Aneurysms: Formation, Progression and Developmental Chronology.” Translational stroke research 5.2 (2014): 167–173. PMC. Web. 3 Apr. 2016.

[2]] "Cerebral Aneurysms." New England Journal of Medicine N Engl J Med 355.25 (2006): 2703-705. Web

[3] Wright, Imelda. "Cerebral Aneurysm—Treatment and Perioperative Nursing Care." AORN Journal 85.6 (2007): 1172-186. Web.

[4] "Intracranial Aneurysms." New England Journal of Medicine N Engl J Med 336.24 (1997): 1758-759. Web.

[5] Shindo A, Sakai N, Sakai H, Higashi T, Nagata I, Kikuchi H, Problems involved in endovascular embolization of intracranial aneurysms with three-dimensional Guglielmi detachable coils,Shindo A, Sakai N, Sakai H, Higashi T, Nagata I, Kikuchi H.
No Shinkei Geka. 2001 Sep;29(9):815-20. Japanese.

[6] Boyle, A.J., T.L. Landsman, M.A. Wierzbicki, L.D. Nash, W. Hwang, M.W. Miller, E. Tuzun, S.M. Hasan, D.J. Maitland. "In vitro and in vivo evaluation of shape memory polymer foam-over-wire embolization device delivered in saccular aneurysm models." Journal of Biomedical Materials Research Part B, DOI: 10.1002/jbm.b.33489, 2015.

[7] Meng, Harper, and Guoqiang Li. "A Review of Stimuli-responsive Shape Memory Polymer Composites." Polymer 54.9 (2013): 2199-221. Web.

[8] Page, Jonathan M., Edna M. Prieto, Jerald E. Dumas, Katarzyna J. Zienkiewicz, Joseph C. Wenke, Pamela Brown-Baer, and Scott A. Guelcher. "Biocompatibility and Chemical Reaction Kinetics of Injectable, Settable Polyurethane/allograft Bone Biocomposites." Acta Biomaterialia 8.12 (2012): 4405-416. Web.

[9] Rodriguez JN, Hwang W, Horn J, Landsman TL, Boyle A, Wierzbicki MA,Hasan SM, Follmer D, Bryant J, Small W, Maitland DJ. 2015. Design and biocompatibility of endovascular aneurysm filling devices. J Biomed Mater Res Part A 2015:103A:1577–1594.

[10] Ratner, B. D., K. W. Gladhill, and T. A. Horbett. "Analysis Ofin Vitro Enzymatic and Oxidative Degradation of Polyurethanes." Journal of Biomedical Materials Research J. Biomed. Mater. Res. 22.6 (1988): 509-27. Web.

[11] Hawkins, W. Lincoln. Polymer degradation and stabilization. Vol. 8. Springer Science & Business Media, 2012.